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Visible light promoted photoredox C(sp^3)–H bond functionalization of tetrahydroisoquinolines in flow†

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A merger of organocatalysis and visible light photoredox catalysis performed in flow allowed access to a wide range of functionalized *N*-aryl-substituted tetrahydroisoquinolines (THIQs) in a formal C–H oxidation/Mannich reaction. Strecker type functionalization and copper-catalyzed alkynylation of several *N*-aryl-substituted THIQs were also successfully performed in flow, giving valuable products with high efficiencies. The use of custom-made porous polymeric type microreactors proved to be crucial regarding the C–H oxidation step and overall reaction performance.

Introduction

The 1,2,3,4-tetrahydroisoquinoline (THIQ) skeleton is considered a privileged structure in medicinal chemistry. It is found in natural and synthetic organic molecules with various biological activities and used for different therapeutic purposes (Fig. 1).[1] Cross-dehydrogenative coupling reactions (CDC) have long been an essential approach for the synthesis of functionalized THIQs.[2] These reactions have mostly been performed by employing high-valent transition-metal catalysts combined with co-oxidants such as *tert*-butylhydroperoxide (TBHP), H_2O_2, or molecular oxygen.[3]

On the other hand, visible light promoted single electron transfer (SET) oxidations of C(sp^3)–H bonds adjacent to the nitrogen atom have proven to be very useful tools for the C1 functionalizations of THIQs. Visible light photoredox catalysis has been one of the fastest growing methodologies in the organic chemistry field in the past decade.[4] Some of the seminal endeavors that showcased high potential for visible light photoredox catalysis and reinvigorated interest in this field were performed by MacMillan,[5] Yoon,[6] and Stephenson.[7] Organic photosensitizers, such as Erythrosine B,[8] eosin Y,[9] or carbon nitride,[10] and metal complexes of Ru and Ir, have found widespread application in the functionalizations of THIQs. Stephenson[11] and Lin[12] demonstrated the oxidative coupling of nitroalkanes or other functionally diverse nucleophiles[13] with *N*-aryl-tetrahydroisoquinolines using Ru and Ir polypyridyl photocatalysts. The Rueping group reported the successful integration of photoredox catalysis and organocatalysis for the direct Mannich reaction of THIQs and ketones with good to excellent yields.[14] The same authors also achieved successful photoredox catalyzed oxidative Strecker reactions[15] and phosphonylations[16] of THIQs. Asymmetric Mannich type functionalizations of THIQs have been achieved combining Ru photoredox catalysis with Co catalysis[17] or with organocatalysis using chiral amino acid as an organocatalyst.[18]

Lately, the application of microfluidic devices has been a very promising strategy in organic chemistry,[19] and one of the research fields in which microfluidics have shown great potential is visible light photochemistry.[20] There are several advantages when conducting transformations in flow compared to batch reactions, in particular: a more predictable reaction scale-up, decreased safety hazards, improved reproducibility and yields, shorter residence time, higher reaction selectivity

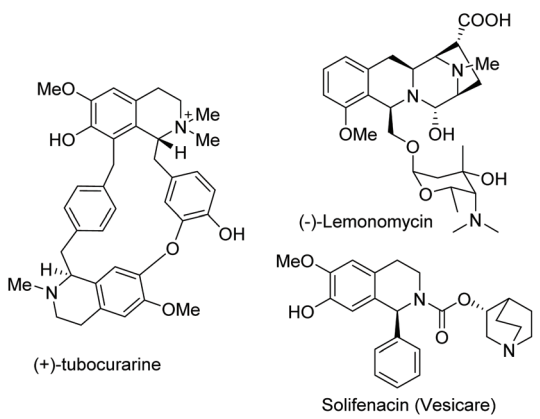

Fig. 1 Biologically relevant THIQs.

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and product purity and lower catalyst loading. In addition, for photochemical transformations, the high surface-area-to-volume ratios typical of flow reactors allow for improved light efficiency. The utilization of microreactors in photochemistry implies that at least one side of the microreactor is transparent. Light penetration in batch reactors is limited by decreasing light transmission over distance in a liquid medium.

Having all these advantages in mind, it comes as no surprise that visible light promoted photoredox chemistry in flow has been applied in functionalizations of THIQs, although scarcely. The Stephenson group used a PFA tubing capillary microreactor for the C–H oxidation of THIQs using super-stoichiometric amounts of $BrCCl_3$ as a terminal oxidant, while the subsequent addition reaction was performed in batch.[21] Zeitler used a microreactor in the photoredox functionalization of THIQs to generate aza-Henry products.[22] However, to the best of our knowledge, there is no comprehensive investigation on the microfluidic functionalization of THIQs using Mannich, Strecker or alkynylation protocols with simple and readily available Ru catalyst and polydimethylsiloxane (PDMS) matrices.

Results and discussion

Mannich type functionalization of THIQs

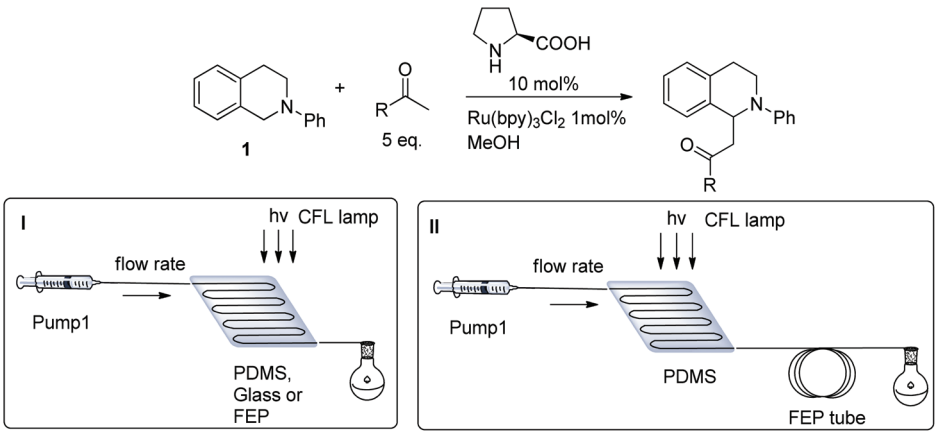
We have recently reported the functionalization of biologically relevant THIQ structures based on DDQ oxidation/Mannich type reaction using proline as an organocatalyst.[23] In continuation of this study, we turned our attention towards more efficient microflow procedures in the CDC reactions of THIQs. Since the DDQ oxidation procedure proved to be inappropriate for miniaturization in microflow systems,[24] we turned our attention towards the applications of visible light promoted photocatalytic protocols for functionalizations of THIQs in flow. Regarding Mannich type functionalization, from previous studies, it is known that the best results in the batch system are obtained when using L-proline as an organocatalyst and Ru $(bpy)_3Cl_2$ as a photocatalyst in acetonitrile as a solvent.[14] However, due to the low solubility of L-proline in acetonitrile,[25] we had to optimize the reaction conditions with regard to the solvent, organocatalyst, photoredox catalyst and light source used (Table S1†). We obtained the best yields when using 1 mol% $Ru(bpy)_3Cl_2$, 8 W CFL lamp, 10 mol% of L-proline and 10 equivalents of ketone in MeOH, which proved to be the best solvent regarding chemical yield and efficiency, while at the same time providing a homogeneous reaction mixture (Table S1†). From our previous work, we knew that significant ee values could not be expected with the organocatalysts we employed;[23] however, they provided high reactivities in our reaction setup.

Upon optimizing the reaction conditions in the batch system, we started testing various microreactor setups to maximize the efficiency of the transformation regarding reaction times and yields. We assembled three experimental designs using microreactors made from (a) silicon and glass, (b) commercially available fluorinated ethylene propylene, FEP and (c) a polydimethylsiloxane (PDMS) microreactor (see the ESI† for details). Firstly, all three reactor types were tested by directly transferring the optimized batch conditions to microfluidic devices. A custom made PDMS type reactor, possessing a 0.76 mm channel diameter, was irradiated using the 8 W CFL lamp. All the reactants were premixed in the dark and pumped through the microreactor with a 1 h residence time. Reaction with acetone as a nucleophile with a catalyst loading of 2 mol% proceeds in reactor setup I, and after 1 h of retention time, 71% conversion is achieved with some unreacted starting material **1** present in the reaction mixture (Table 1, entry 2). An increase of the retention time to 2 h gave 91% of the desired material (Table 1, entry 3). Decrease of the catalyst loading to 1 mol% and keeping retention time at 2 h, to our delight, gave us 88% yield of the desired product (Table 1, entry 4).

Under the same conditions, a FEP type microreactor with an internal diameter of 0.76 mm gave very low yields of the desired products regardless of the light source that was applied (Table 1, entries 5–7). Lastly, a glass–silicon type reactor under the same conditions gave 30% and 31% yields in 30 min and 120 min residence times, respectively (Table 1, entries 8 and 9). Since in this type of reaction, oxygen acts as the terminal oxidant, we believe that the porosity of the PDMS matrix for gases[26] is one of the reasons this reactor type performed much better than the other two reactor types in this particular setup. Thin PDMS layers have previously been used in the photooxygenation reactions in flow as gas porous membranes.[27] Another reason for better performance of the PDMS reactor might be increased light penetration through more transparent or thinner reactor walls to the reaction channels and hence a higher rate of oxidation reaction compared to those of other types of reactors. When our reaction conditions were tested with less reactive ketones such as acetophenone, after 2 h of retention time 63% yield of the desired product was obtained; however, complete conversion to iminium ions was observed (Table 1, entry 10). Since oxidation proceeded efficiently and the limiting step is an enamine addition step, the FEP tube microreactor was attached as a continuation of the PDMS reactor, which allowed an increase of the retention time to 6 h (2 h PDMS for the oxidation step + 4 h FEP for the addition step) and to our delight 83% of the desired product was isolated (Table 1, entry 10, reactor setup II). This reaction setup allowed the oxidation reaction to be performed in the PDMS reactor, while a subsequent addition reaction took place in the FEP tube reactor.

These results showed that microreactors could be used to efficiently functionalize biologically relevant THIQ compounds. Microfluidic setups were optimized depending on the reactivity of the nucleophilic reaction partner. Photocatalyzed oxidation of THIQ proceeded in approximately 2 h using the 8 W CFL lamp, while the enamine addition step can be a limiting factor when sterically hampered and less reactive ketones are used as nucleophilic components of the reaction. Using these optimized conditions, we tested the reactivities of variously substituted THIQs with several ketones (Table 2).

Table 1 Transfer of the visible light photoredox THIQ oxidation/organocatalyzed Mannich reaction to microfluidic setups



Entry[a]	Ketone	Microreactor setup	Reactor type	$Ru(bpy)_3Cl_2$ (mol%)	Retention time (h)	Light source	Yield[b] (%)
1	Acetone	—	Batch	1	24	8 W	85
2	Acetone	I	PDMS	2	1	8 W	71
3	Acetone	I	PDMS	2	2	8 W	91
4	Acetone	I	PDMS	1	2	8 W	88
5	Acetone	I	FEP	1	2	8 W	19
6	Acetone	I	FEP	1	2	15 W	20
7	Acetone	I	FEP	1	2	Blue LED	20
8	Acetone	I	Glass	1	0.5	8 W	30
9	Acetone	I	Glass	1	2	8 W	31
10	Acetophenone	I	PDMS	1	2	8 W	63
11	Acetophenone	II	PDMS + FEP	1	2 + 4	8 W	83

[a] Reaction conditions: tetrahydroisoquinoline (0.25 mmol, 1 equiv.), $Ru(bpy)_3Cl_2$ (0.0025 mmol, 1 mol%), L-proline (0.075 mmol, 0.3 equiv.) and acetone (10 equiv.) were added to the solvent (1 mL) and pumped through the microfluidic device irradiated with the CFL lamp; a residence time of 2 h was applied. [b] Isolated yields after column chromatography.

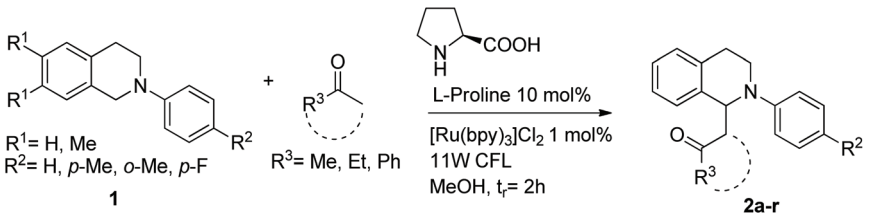
N-Phenyl, N-*p*-tolyl, *N*-*p*-F-C_6H_4 and *N*-*p*-MeO-C_6H_4 substituted THIQs were tested. *N*-Aryl groups stabilize the reactive intermediates in cross-dehydrogenative couplings,[28] and these tertiary substituted substrates proved to be the best choice in this reaction setup. Moreover, *N*-*p*-MeO-C_6H_4 protection can be easily removed,[29] thus allowing access to unsubstituted functionalized THIQs. As the nucleophilic partners, several ketones were tested: acetone, ethyl methyl ketone and acetophenone (Table 2). In general, reactions with acetone proceeded most efficiently giving the best yields among the tested ketones using microreactor setup I. Ethyl methyl ketone required microreactor setup II to be used for best yields; it possesses 2 enolizable positions, but reacts exclusively at the less substituted side of the molecule to give products in very good yields (Table 2, entries 2, 6, 9, 12 and 15). Acetophenone reacts efficiently using microreactor setup II, giving very good yields of products in all cases (Table 2, entries 2, 5, 8, 11 and 14). Unprotected THIQs did not react under these conditions in our microreactor setup.

We propose the following plausible mechanism for the visible light promoted photoredox catalyzed C–H oxidation/organocatalyzed Mannich reaction (Scheme 1). Radical cation **II** is formed by single-electron oxidation of **I** by the excited state of $Ru(bpy)_3^{2+}$, creating the powerful reducing agent Ru^+ [Ru(II)/Ru(I) −1.33 V *vs.* SCE]. Catalyst turnover may be accomplished by the reduction of adventitious oxygen and/or acetone to its radical anion.[11] This radical anion may abstract a hydrogen atom from the trialkylammonium radical cation **II** to form the desired iminium ion, **III**. The iminium ion enters the organocatalytic cycle and undergoes Mannich type addition of enamine **V** formed in the reaction of organocatalyst **IV** with a ketone. Addition adduct **VI** hydrolyzes to give the observed product and to release the organocatalyst which enters the new catalytic cycle. Very low reactivity in the FEP or glass microreactors provides us with a reason to believe that oxygen is crucial for the catalyst turnover as the best yields are obtained in the PDMS matrices, which are porous for gases.

Cyanation of THIQs

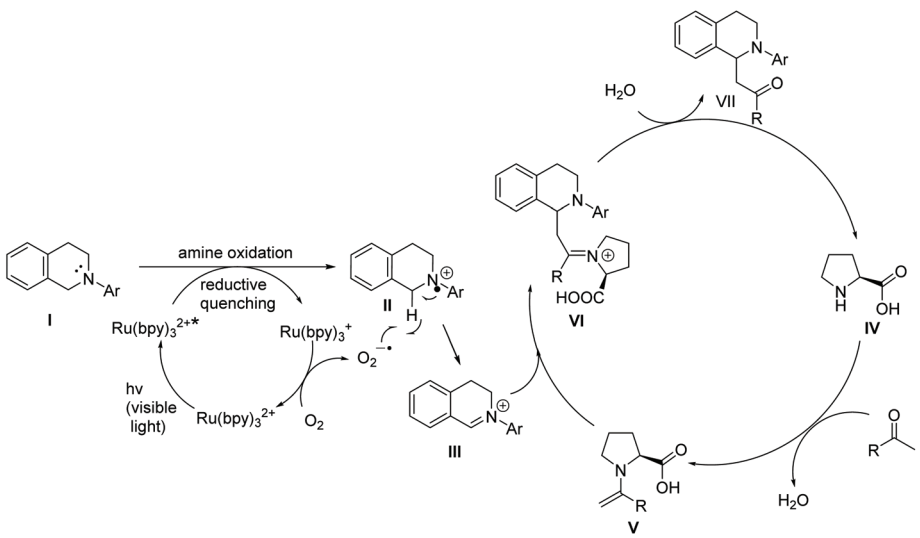
To expand the scope of microflow methodology, we turned our attention to other formal oxidative coupling partners. Cyanation, *i.e.* the Strecker type functionalization of THIQs, gives access to important structural scaffolds. Further transformations of Strecker adducts offers access to important building blocks, such as α-amino acids, vicinal diamines, α-amino aldehydes, and α-amino ketones. This versatility makes synthesis in continuous flow very attractive. There are reports on photoredox cyanation using an $Ir(ppy)_3$ catalyst and TsCN,[30] and reports on photoredox functionalization of THIQs in flow with TMSCN and Rose Bengal as a photoredox sensitizer.[31] As

Table 2 The merger of organocatalysis and photoredox catalysis in the THIQ oxidation/Mannich reaction in flow



Entry[a]	R1	R2	Ketone	Microreactor setup	Time (h)	Yield[b] (%)
1	H	H	Acetone	I	2	88 (**2a**)
2	H	H	Methyl ethyl ketone	II	2 + 4	89 (**2b**)
3	H	H	Acetophenone	II	2 + 4	83 (**2c**)
4	H	F	Acetone	I	2	95 (**2d**)
5	H	F	Methyl ethyl ketone	II	2 + 4	85 (**2e**)
6	H	F	Acetophenone	II	2 + 4	84 (**2f**)
7[c]	H	OMe	Acetone	I	2	88 (**2g**)
8[c]	H	OMe	Methyl ethyl ketone	II	2 + 4	79 (**2h**)
9[c]	H	OMe	Acetophenone	II	2 + 4	70 (**2i**)
7	OMe	H	Acetone	I	2	95 (**2j**)
8	OMe	H	Methyl ethyl ketone	II	2 + 4	89 (**2k**)
9	OMe	H	Acetophenone	II	2 + 4	73 (**2l**)
10	OMe	Me	Acetone	I	2	83 (**2m**)
11	OMe	Me	Methyl ethyl ketone	II	2 + 4	75 (**2n**)
12	OMe	Me	Acetophenone	II	2 + 4	71 (**2o**)
13	OMe	F	Acetone	I	2	84 (**2p**)
14	OMe	F	Methyl ethyl ketone	II	2 + 4	86 (**2r**)
15	OMe	F	Acetophenone	II	2 + 4	73 (**2s**)

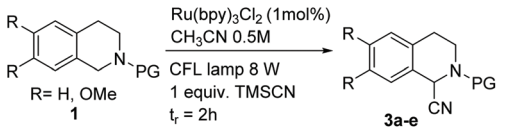
[a] Reaction conditions: tetrahydroisoquinoline (0.25 mmol, 1 equiv.), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (0.0025 mmol, 1 mol%) and L-proline (0.075 mmol, 0.1 equiv.) were added to MeOH (1 mL) and ketone (excess) was added. The reaction mixture was pumped through the microfluidic device. The system was irradiated using the CFL lamp, and a residence time of 2 h was applied. See the ESI† for details. [b] Isolated yields after column chromatography. [c] Reactions performed in a 1 : 1 mixture of MeOH : CH_3CN due to the low solubility of the starting material in MeOH.

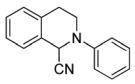
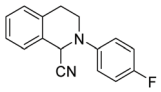
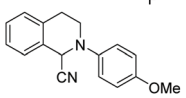
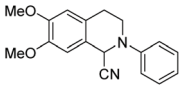
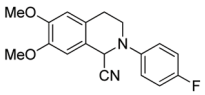
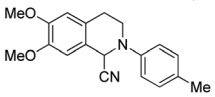


Scheme 1 Plausible catalytic cycle.

the extension of our methodology, we tested the C–H oxidation/Strecker reaction using TMSCN as the source of CN^- ions in our microreactor setup I. The addition of CN^- to the *in situ* formed iminium ion is a very fast process and a retention time of 120 min is sufficient for the reaction to complete (Table 3). All products were obtained in very good yields with full conversions of the starting material (Table 3, entries 1–6). The reaction times are much shorter compared to the batch conditions.[32] Even excess of TMSCN is well tolerated as the byproducts are volatile and easily removed from the reaction mixture.

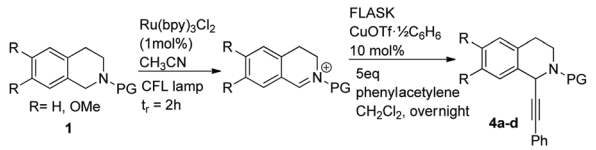
Table 3 Visible light photoredox Strecker reaction conducted under flow conditions

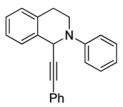
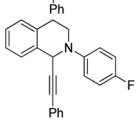
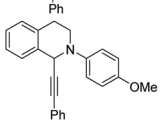
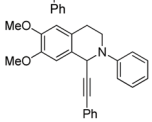
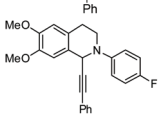
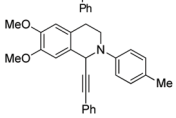


Entry[a]	Product	Residence time (h)	Light source	Yield[b] (%)
1		2	8 W	95% (**3a**)
2		2	8 W	89% (**3b**)
3		2	8 W	84% (**3c**)
4		2	8 W	Quant (**3d**)
5		2	8 W	91% (**3e**)
6		2	8 W	85% (**3f**)

[a] Reaction conditions: tetrahydroisoquinoline (0.25 mmol, 1 equiv.), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (0.0025 mmol, 1 mol%) and trimethylsilyl cyanide (0.3 mmol, 1.2 equiv.) were added to CH_3CN (1 mL) and pumped through the microfluidic device. The system was irradiated with the CFL lamp, and a residence time of 2 h was applied. [b] Isolated yields after column chromatography.

Table 4 Visible light photoredox alkynylation conducted under flow conditions



Entry[a]	Product	Residence time (h)	Light source	Yield[b] (%)
1		2	11 W	99 (**4a**)
2		2	11 W	88 (**4b**)
3		2	11 W	82 (**4c**)
4		2	11 W	85 (**4d**)
5		2	11 W	80 (**4e**)
6		2	11 W	90 (**4f**)

[a] Reaction conditions: tetrahydroisoquinoline (0.25 mmol, 1 equiv.) and $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (0.0025 mmol, 1 mol%) were added to CH_3CN (1 mL) and pumped through the microfluidic device irradiated with the CFL lamp, and a residence time of 2 h was applied. The recipient flask contained $CuOTf{\cdot}\frac{1}{2}C_6H_6$ (0.025 mmol, 0.1 equiv.) and phenylacetylene (1.25 mmol, 5 equiv.) in 1 ml CH_2Cl_2. The combined reaction mixture was stirred overnight. [b] Isolated yields after column chromatography.

Alkynylation of THIQs

Alkynylation of THIQs under flow conditions is not a straightforward task as cyanation since Cu catalysts commonly used in this transformation have low solubility in solvents best fitted for photoredox catalysis. Upon thorough optimization (Table S2, ESI†), we found that the best results are obtained when the oxidation step is performed in the PDMS reactor and the alkynylation step is performed in the recipient flask. Mixing all the reactants and pumping them simultaneously through the flow reactor led to inconsistent results due to the heterogeneous reaction composition, which was very often accompanied by reactor clogging. Hence, the stepwise procedure, *i.e.*, separation of reaction steps, is the best fit for this type of functionalization. A 2 h residence time in the microreactor and overnight stirring of the formed iminium ions with the alkynylation reagents in the recipient flask give the desired products in very good yields (Table 4). Several Cu catalysts were tested, and $CuOTf{\cdot}\frac{1}{2}C_6H_6$ (10 mol%) in conjunction with five equivalents of phenylacetylene dissolved in CH_2Cl_2 in the recipient flask was found to be the best combination regarding reaction yield. Several substrates were tested under optimized conditions and they gave excellent yields of the desired products (Table 4, entries 1–6). This type of reaction setup opens up an opportunity to use oxidized THIQ from the microreactor and distribute it in several flasks containing different alkyne components, thus allowing rapid parallelization using only a single microfluidic device. There are methods to avoid reactor clogging and issues with heterogeneous reaction compositions by applying specific microreactor setups[33] and this will be one of the future tasks in our research. The mechanism of photoredox catalyzed alkynylation has already been proposed elsewhere[34] as well as the flow system that used super-stoichiometric amounts of $BrCCl_3$ as a terminal oxidant for catalyst turnover.[21]

Conclusion

The application of microfluidic devices for visible light promoted photoredox reactions is a big step forward in improving

the practicality of CDC coupling reactions that have high importance in the functionalization of biologically active structures such as THIQs. Shorter reaction times, possible parallelization and higher efficiency are the main characteristics of this new process. The use of microfluidic devices in the visible light promoted photoredox oxidation of THIQs/Mannich reaction of enamines formed *in situ* from ketones and secondary amine organocatalysts tremendously improved the reaction times and yields of this domino process. Besides the Mannich reaction, the Strecker type addition of TMSCN to the iminium ion (formed *in situ*) can also be performed with tertiary aryl-substituted THIQs using microflow conditions. In addition, copper-catalyzed alkynylation of THIQs in flow was effectively performed. These procedures represent a powerful method to form new carbon–carbon bonds directly from two different C–H bonds under oxidative conditions in flow. The use of custom-made polydimethylsiloxane (PDMS) type microreactors proved to be crucial regarding the success of the C–H oxidation step and the overall reaction performance, *i.e.*, the reaction rate and yields. The porosity of PDMS for gases and oxygen, in particular, proved to be crucial for the catalyst turnover and overall success of this reaction setup.

Experimental section

General procedure for THIQ oxidation/Mannich reaction

Tetrahydroisoquinoline (0.25 mmol, 1 equiv.), Ru cat. (0.0025 mmol, 1 mol%), L-proline (0.0025 mmol, 0.1 equiv.) and ketone (5–10 equiv.) were added to MeOH (1 mL) and pumped through a microfluidic device using a syringe pump. The system was irradiated with a CFL lamp; the residence time that was applied depended on the type of nucleophile (2 h or 6 h). Upon completion of the reaction, the excess of the solvent was evaporated under reduced pressure on a vacuum evaporator. The crude residue was subjected to ^{1}H NMR analysis. Purification was performed using SiO_2 column chromatography with petroleum ether/ethyl acetate as eluents.

General procedure for THIQ oxidation/Strecker reaction

Tetrahydroisoquinoline (0.25 mmol, 1 equiv.), Ru cat. (0.0025 mmol, 1 mol%) and TMSCN (0.25 mmol, 1 equiv.) were added to acetonitrile (1 mL) and pumped through the microfluidic device using a syringe pump. The system was irradiated with the CFL lamp, and a residence time of 1 h was applied. Upon completion of the reaction, the excess of the solvent was evaporated under reduced pressure on the vacuum evaporator. The residue was subjected to ^{1}H NMR analysis. Purification was performed using SiO_2 column chromatography with petroleum ether/ethyl acetate as eluents.

General procedure for THIQ oxidation/alkynylation reaction

Tetrahydroisoquinoline (0.25 mmol, 1 equiv.) and Ru cat. (0.0025 mmol, 1 mol%) were added to acetonitrile (1 mL) and pumped through the microfluidic device using a syringe pump. The system was irradiated with the CFL lamp, and a residence time of 2 h was applied. Subsequently, in the recipient flask were added phenylacetylene (1.25 mmol, 5 equiv.) and the Cu catalyst (0.025 mmol, 0.1 equiv.) in CH_2Cl_2 and the mixture was stirred at room temperature overnight. Upon completion of the reaction, the excess of the solvent was evaporated under reduced pressure on the vacuum evaporator. The residue was subjected to ^{1}H NMR analysis. Purification was performed using SiO_2 column chromatography with petroleum ether/ethyl acetate as eluents.

Characterization data for the new compounds

Compound (2o). Prepared as shown in the general experimental procedure. 71% as yellowish oil. R_f = 0.53 (petroleum ether/EtOAc : 3/1); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.84 (d, J = 8.2 Hz, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 7.7 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.69 (s, 1H), 6.61 (s, 1H), 5.50 (t, J = 4 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.69–3.60 (m, 1H), 3.58–3.46 (m, 2H), 3.35 (dd, J = 16.1, 7.2 Hz, 1H), 3.02 (ddd, J = 15.6, 9.6, 5.7 Hz, 1H), 2.76 (dt, J = 16.0, 4.3 Hz, 1H), 2.23 (s, 3H); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 199.2, 147.7, 147.2, 146.9, 137.4, 133.0, 130.4, 129.8, 128.5, 128.1, 127.8, 126.2, 115.5, 111.3, 109.9, 55.8, 55.4, 44.8, 42.1, 26.9, 20.3; **IR** (ATR): ν = 2987 (m), 2834 (m), 1679 (s), 1612 (m), 1514 (vs), 1449 (m), 1273 (s), 1249 (s), 1116 (m), 1021 (m); **HRMS**: m/z (ESI/TOF) calcd for $C_{26}H_{27}NO_3$ (M+) 401.1991, found 401.1990.

Compound (4e). Prepared as shown in the general experimental procedure. 80% as yellowish oil. R_f = 0.24 (petroleum ether/EtOAc : 7/1); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.31–7.17 (m, 5H), 7.11–7.05 (m, 2H), 7.05–6.98 (m, 2H), 6.84 (s, 1H), 6.66 (s, 1H), 5.46 (s, 1H), 3.90 (s, 1H), 3.88 (s, 1H), 3.62–3.56 (m, 2H), 3.11–3.02 (m, 1H), 2.84 (dt, J = 15.9, 3.2 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 158.7, 156.8, 148.6, 147.9, 146.7, 131.9, 128.4, 127.2, 126.3, 123.1, 119.8, 119.7, 115.8, 115.6, 111.6, 110.4, 88.5, 85.5, 56.3, 56.1, 53.7, 44.3, 28.7; **IR** (ATR): ν = 2933 (w), 2833 (w), 1611 (w), 1509 (vs), 1463 (m), 1247 (s), 1118 (s), 1027 (w), 816 (w); **HRMS** (ESI) m/z calculated for $C_{25}H_{22}FNO_2^+$ ([M+]) 387.1635, found 387.1631.

Compound (4f). Prepared as shown in the general experimental procedure. 90% as yellowish oil. R_f = 0.29 (petroleum ether/EtOAc : 7/1); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.33–7.26 (m, 2H), 7.25–7.18 (m, 3H), 7.15–7.08 (m, 2H), 7.06–7.01 (m, 2H), 6.84 (s, 1H), 6.65 (s, 1H), 5.51 (s, 1H), 3.88 (d, J = 11 Hz, 6H), 3.73–3.56 (m, 2H), 3.06 (ddd, J = 16.6, 10.5, 6.4 Hz, 1H), 2.85–2.78 (m, 1H), 2.29 (s, 3H); **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 148.2, 147.6, 147.5, 131.7, 129.6, 129.4, 128.0, 127.9, 127.3, 126.3, 123.1, 117.6, 111.4, 110.2, 88.7, 84.9, 56.1, 55.9, 52.7, 43.7, 28.4, 20.45; **IR** (ATR): ν = 3000 (m), 2917 (m), 2832 (m), 1612 (m), 1516 (vs), 1463 (s), 1407 (s), 1260 (s), 1248 (s), 1213 (s), 1117 (s); **HRMS** (ESI) m/z calculated for $C_{26}H_{25}NO_2^+$ ([M+]) 383.1885, found 383.1878.

Full characterization data for all compounds are given in the ESI.†

Conflicts of interest

There are no conflicts to declare.

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